Mercer-style cascade impactors separate aerosol particles into eight size ranges as the sample is drawn through a series of stages with jets and the particles impact on the glass collection plates. The effective cut-off diameters of the stages vary from about 0.2 to 4 μm. The amount of material collected on each impaction stage will be determined by UV/PM chemical analysis.

A wide size range will be covered with these three techniques, which will enable us to choose the method most applicable to the aerosol system. It is estimated that most of the particles in the aging room and the exposure atmosphere will be between 0.1 to 1.0 μm in size. Assuming that the performance of the Model HSLAS-065 with RASS is verified during the prestart effort, BNW proposes to use this optical particle counter routinely during the subchronic and chronic studies to monitor particle size distribution in the aging room and exposure units.

The method for monitoring the particle size distribution of DEE will be selected during the prestart phase in a manner similar to the RASS study. DEE is expected to have a somewhat larger particle size distribution. It is anticipated that a combination of the optical particle counter and the cascade impactor will be used for routine monitoring.

Combustion aerosols such as cigarette smoke and diesel engine exhaust are very complex systems with thousands of components. Their aerosol properties are time-dependent, with continuous transfer of material between particulate and vapor phases, as well as between particles of different sizes. Highly concentrated aerosol systems undergo coagulation, which can reduce the number of particles and increase the average particle diameter. Volatile components can be lost from the particulate phase upon dilution. It is also expected that the chemistry of the combustion particles will vary somewhat with particle size.

In the light of these complexities, when size-distribution data are reported, the dilution level, the age of the smoke, and details and shortcomings of the measurement technique should be clearly stated. During the prestart phase, we intend to evaluate the techniques mentioned above and choose the most applicable and repeatable methods for the routine analysis of particle size distribution in our exposure chambers. It is likely that the particle size data will not be absolute or definitive, but it should provide a means to evaluate the consistency of the aerosol particle size distribution throughout the studies.

c. Environmental

(1) Temperature. Temperatures will be measured using T-type thermocouples connected to the data acquisition and control system. Temperatures from the aging room, at a single port of each exposure unit, in each exposure unit cabinet, and from the animal housing room will be automatically recorded. Calibration of this system will be accomplished by comparison with a certified mercury thermometer and a temperature-controlled water bath.

(2) Relative Humidity (RH). The RH will be calculated from the temperature measured by a thermocouple and the dew point measured by an EG&G Model 911 DewAll digital humidity analyzer (EG&G, Burlington, MA). A single hygrometer will be multiplexed to the various measurement locations with a computer-controlled valve system. RH from the aging room, at a single port of each exposure unit, and from all animal housing rooms will be automatically recorded. The humidity analyzer will be calibrated by comparison to a certified, portable, EG&G Model 911 dew-point hygrometer.

(3) Air Flow. System air flows will be determined by measuring the pressure drop across calibrated orifices or venturis using a single Validyne Model CD-12 carrier demodulator transducer (Validyne, Northridge, CA) interfaced to a Validyne Model MP-45 pressure transducer. This system will be calibrated by a Dwyer Mark II (Dwyer, Michigan City, IN) water manometer. Exposure unit inlet and exhaust flows, as well as distribution line flows, will be measured by a single-pressure transducer multiplexed to the various measurement locations with a computer-controlled valve system. Flow will be automatically

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recorded at each location. The flow system will be calibrated by comparison to a certified flow calibration unit.

(4) Sound Level. Sound levels will be measured in both the animal exposure rooms and the DEE room. Measurements in the engine room will be made to determine if ear protection will be required for workers in the room. Measurements in the animal rooms will be made to assure that the exposure equipment does not generate sound levels that could significantly contribute to animal stress. Sound levels will be measured during a period of normal activity with all exposure generation equipment operating. Both A-weighted and flat-frequency measurements will be taken, the latter being more appropriate for interpreting noise levels heard by rodents. The former, which more closely approximates the sensitivity of the human auditory system, will be included as a reference for interpreting noise levels sensed by humans.

The measurements will be made with a precision integrating sound level meter (Model 1988, General Radio, Concord, MA) with a ½-inch random incidence microphone. The frequency response of this meter is 5 Hz to 20 kHz. This instrument meets the requirements of ANSI Standard S1.4-1971 for Type 1 sound level meters and ANSI Standard S1.11-1966 for octave band filter sets. The meter will be calibrated on the day of the measurement using a General Radio 1986 Omnical sound level calibrator at 1000 Hz.

2. Prestart Validation

a. Temporal Stability

(1) Total Particulate Matter (TPM). Although the TEOM will not be used to report average concentration for the 6-hour exposure period (gravimetric or UV analysis of filter samples will be used for this purpose), its response will be used to indicate the relative concentration during the course of an exposure and will be used as feedback for manual control of the exposure concentrations. A single TEOM will be dedicated to monitoring the DEE exposure unit pair while a second TEOM will be multiplexed to monitor the RASS and filtered-air exposure unit pairs. The TEOM aerosol concentration measurements will be made in one of each RASS and DEE exposure unit pair twice/hour. These measurements will be used to demonstrate and control the temporal stability of the aerosol mass concentration during the exposure period. The average TPM concentrations will be controlled to within ±20% of the target value. The variation in daily concentration will be controlled to within ±20% relative standard deviation (RSD) from the mean. Prior to the start of each study, concentration stability within the desired target range will be demonstrated during three successive exposure days.

Before the start of each study, the concentration buildup and decay times in the aging room and the RASS exposure units will be determined from TEOM measurements. For these measurements, the TEOM will sample from the RASS distribution tube as it exits the aging room or from each single exposure unit approximately once every 2 minutes. The time for the concentration to reach 90% of its target value at the start of the exposure (T_{90}) and the time for it to decay to 10% of the target value at the end of the exposure (T_{10}) will be reported. The RASS generation system will be operated for sufficient time to achieve stable concentration in the aging room before the start of animal exposures. Due to the cycling nature of the DEE generation system, no buildup and decay times will be determined for the DEE exposure units; however, the DEE generation system will be operated for one engine cycle prior to the start of animal exposure. Both RASS and DEE animals will be exposed for a period of 6 hours plus T_{90} (T_{90} will be determined only for RASS and will be used for the entire study).

The relative aerosol mass concentration in the RASS aging room will be monitored by a RAM dedicated to this purpose. RAM readings will be recorded at ~15-minute intervals during the concentration buildup period and during the 6-hour exposure period.

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(2) Carbon Monoxide (CO). Carbon monoxide will not be used as a concentration control parameter; however, CO concentration, in combination with aerosol concentration as determined by the TEOM, can be an excellent tool for recognizing and diagnosing possible problems with the test article generation and distribution systems. CO concentration measurements will be made in one of each RASS and DEE exposure unit pair twice per hour during exposure. If the generation and delivery systems are functioning properly, variations in CO concentration should be directly proportional to variations in aerosol concentration.

During prestart validation, the normal relationship between CO concentration and aerosol concentration will be determined.

(3) Aerosol Particle Size. To assure that the particle size distribution is not affected by the generation and distribution system during the course of an exposure, particle size analysis will be performed from a single port from the high-concentration DEE and RASS exposure units during the first and last hour of a typical exposure period. The diesel engine will be run at a constant speed and load during this test to eliminate the temporal variation in DEE concentration.

b. Spatial Uniformity

(1) Total Particulate Matter (TPM) and Carbon Monoxide (CO). The spatial uniformity of the aerosol and CO concentrations within the exposure unit will be determined by measuring the aerosol mass using the TEOM and the CO using the CO monitor. Concentrations will be measured at one exposure port on each level of each exposure unit. The diesel engine will be run at a constant speed and load during this test to eliminate the temporal variation in DEE concentration.

(2) Aerosol Particle Size. Prior to the start of each study, particle size measurements will be made at a single exposure port at the top, middle and bottom of each exposure unit during routine generation to establish the particle size distribution of the aerosol and to demonstrate spatial uniformity.

c. Exposure Atmosphere Characterization. The exposure atmosphere for RASS and DEE will be characterized by performing the chemical-specific measurements cited in Table IV-4. The validation of these methods and associated measurements will be summarized in the prestart report. Finalized SOPs for each of the cited measurements will also be included in the prestart report.

Particle Size. Particle size distribution measurements will be repeated at one port per exposure unit once during the subchronic study and at least once per month during the chronic study.

D. EXPOSURE DATA ACQUISITION AND CONTROL

1. System Description

The main data acquisition and control system for the studies will consist of an Apple Macintosh computer interfaced with an HP Model 3497A data acquisition control unit (Hewlett-Packard, Hollywood, CA). Input from analog instruments and thermocouples will be interfaced using HP analog input cards. HP digital input cards will be used to monitor alarm conditions and on/off status devices. HP digital actuator cards will operate control relays.

System software has been developed using LabVIEW (National Instruments, Austin, TX) data acquisition, analysis, and presentation software. This programming application uses the computer display for both a control interface and data display. A mouse is used to "point and click" on virtual control elements such as "buttons" and "switches" that appear on the display screen. The software allows each exposure group to be exposed independently of the other groups, allowing staggered start times.

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Specific information relating to the data acquisition program (such as instrument assignments, measurement frequencies, calibration parameters, alarm limits, and alarm reactions) will be entered into spreadsheet-like display windows on the computer screen. To assure GLP compliance, any changes in these values will result in a printout of the old window, the new window, the date, operator's name, and a comment field for explaining the change. Changes will be highlighted in the new window.

Alarm settings include noncritical and critical, upper and lower alarm limits for each data type at each measurement location. The response to particular alarm situations is defined by data alarm response types that can be assigned to any location for each of the four possible alarm conditions. Each alarm response is a self-contained subprogram that, when invoked, will take the appropriate action at the location from which it was called. All data that exceed alarm limits will be printed and stored.

Data will be stored to disk and printed to paper as they are collected, thus assuring minimal data loss in the event of a system failure. Due to the relative durability of paper, the printed record will be officially considered the raw data. The following information will be printed for each measurement: time of acquisition, raw data value, calculated data value, units of measurement, identification of the type of data, the measurement location, and any indication of alarm limits exceeded. At the end of each exposure day, all data recorded to disk will be copied to a central file server over a local area network. These files will be write-protected (i.e., the data cannot be changed in these files). The files on the file server will be routinely backed up on streaming tape. Data editing and analysis will be performed only on backup editing files by qualified and authorized personnel.

Table IV-12 lists the parameters that will be recorded by the data acquisition system, as well as the monitoring locations and recording frequency. The on-line monitoring devices are described in Section IV.C.1.

2. Data Analysis

Exposure data analyses and summations will be performed using spreadsheets and macro routines (Excel, Microsoft Corporation, Redmond, WA) developed at BNW.

3. System Documentation and Validation

System description documentation and SOPs will be written to cover description, operation, calibration, validation, and verification of all exposure systems; data acquisition and control systems and software; and data analysis software. Documentation and validation will satisfy the U.S. EPA GLP Toxic Substance Control Act regulations, 40 CFR 792.

E. INDUSTRIAL HYGIENE AND SAFETY

Throughout the course of the studies, BNW will protect the health and safety of personnel involved and will comply with pertinent environmental protection requirements. Health and safety planning begins with the design of the logistics and the physical layout, with emphasis on the use of engineering controls to contain diesel fuel vapors, diesel exhaust, cigarette smoke, and titanium dioxide, and prevent their escape into the work space. The effectiveness of engineering controls will be ascertained by room air monitoring using continuous, real-time instruments. Concentration readings in excess of the action level (one-half the TLV) will trigger an audible alarm and immediate shutdown of the generation system. Sampling will also be performed initially to monitor the presence of diesel fuel vapors in the room air to ensure that no fuel leaks into the work space. Room air monitoring will be performed throughout the studies in Rooms 511, 519, 523, and 531.

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TABLE IV-12. On-Line Monitoring Parameters

Parameter	Monitor	Location	Number of Locations	Recording Frequency (per Hour)
Temperature	Thermocouple	Exposure Unit	10	once
		Exposure Unit Cabinet	10	once
		Exposure Room	2	once
		Animal Room	1	once
		RASS Generator Room	1	once
		RASS Aging Room	1	once
Relative Humidity	Hygrometer	Exposure Unit	10	once
		Animal Room	1	once
		RASS Generator Room	1	once
		RASS Aging Room	1	once
Air Flow	Orifice Meter	Exposure Unit Inlet	10	once
		Exposure Unit Exhaust	10	once
	Venturi	RASS Aging Room Flow	1	once
		DEE Distribution Line Flow	1	once
~TPM	TEOM "A"	RASS Exposure Unit Pair	3	twice
	TEOM "A"	FA Exposure Unit Pair	1	twice
	TEOM "B"	DEE Exposure Unit Pair	1	twice
	RAM	RASS Aging Room	1	twice
CO	CO "A"	RASS Exposure Unit Pair	3	twice
	CO "A"	FA Exposure Unit Pair	1	twice
	CO "A"	Generator & Exposure Rooms	5	twice
	CO "B"	DEE Exposure Unit Pair	1	twice

KEY: CO = Carbon monoxide; DEE = Diesel engine exhaust; FA = filtered-air; RAM = Realtime aerosol monitor; RASS = Room-aged sidestream cigarette smoke; TEOM = tapered element oscillating micro-balance mass monitor; TPM = Total particulate matter

Carbon monoxide is a chemical compound commen in both diesel exhaust and cigarette smoke. Personnel exposure sampling will involve breathing-zone sampling of CO, in lieu of sampling a wide variety of chemicals that may be present in the two test materials. Results of CO sampling will be used as an index to estimate personnel exposure to other major chemical components in diesel exhaust and cigarette smoke, e.g., aldehydes, NO_x, CO_2, and hydrocarbons. Correlation of CO to these other major chemical components will be done during prestart activities. No attempts will be made to distinguish the contribution of diesel exhaust generated CO exposure from that of cigarette smoke.

The extent of personnel breathing-zone exposure to CO will be initially characterized based on the exposure assessment strategy developed by the American Industrial Hygiene Association (1991). Once exposure characterization is complete, subsequent sampling will be performed periodically for surveillance or under special circumstances. Breathing-zone sampling results may be supplemented by means of

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monitoring CO concentrations in the exhaled air at the end of work shift as recommended by the American Conference of Governmental Industrial Hygienists (1992). Personnel breathing-zone exposure to carbon monoxide will be monitored in Rooms 511 and 519 and occasionally in Rooms 523 and 531.

In addition to potential exposure to test chemicals, excessive noise levels may also present a hazard to personnel in the diesel engine room and therefore will be evaluated. If a noise hazard does exist [>85 dB(A)], applicable Occupational Safety and Health Administration (OSHA) hearing conservation program requirements will be followed (29 CFR 1910.95). Personnel will be provided appropriate hearing protection and caution signs will be posted at the entrance(s) to the rooms. Since personnel entering the diesel engine room stay for only brief periods to start, stop, or service the engine, noise exposure will be minimal. Nevertheless, appropriate hearing protection will be required and room access will be restricted.

Where engineering controls may not always be completely effective, the protection of personnel may be supplemented by establishing certain safe work procedures supported by training and using personal protective equipment. Personnel involved in this study will be provided training to comply with the OSHA requirements for hazard communication (29 CFR 1910.1200 and 1450). A health and safety protocol will be developed and posted in the study area. This protocol will describe available data on health and safety effects from exposure to the test materials, level of personal protection needed, waste disposal requirements, spill control and emergency procedures.

Related health and safety considerations will include fire protection, proper air balance in the work spaces, and prevention of environmental releases.

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V. ANIMAL CARE PROCEDURES

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V. ANIMAL CARE PROCEDURES

A. ANIMAL FACILITIES, PATHOGEN CONTROL PROCEDURES, AND ANIMAL CARE PERSONNEL

1. Animal Facilities and Equipment

LSL-II is designed primarily for large life span inhalation studies in rodents. The laboratory provides spacious animal rooms in a two-corridor (regulated/clean) layout. Traffic into animal housing and exposure areas is strictly controlled with access only from the clean corridor. Monitoring and other study support functions are conducted remotely when appropriate in order to reduce equipment and personnel traffic in the animal areas. Total animal space in LSL-II is 15,500 ft^2. An additional 5,700 ft^2 of animal care support space is used for the cage washing facilities, change rooms, offices, storage areas, and exposure suite control rooms (Figure IV-1).

Major equipment (heating, cooling, and ventilation) is provided in duplicate or with other back-up. The building contains a large diesel-powered generator that can maintain normal temperatures and good ventilation in the animal facility if normal electrical power is lost. All essential systems are on a routine monitoring and preventative maintenance schedule.

The ventilation system provides approximately 18 air changes/hour to animal rooms in the facility. Air pressure differentials within the facility are such that the clean corridor remains positive to the animal rooms, which are positive relative to the regulated corridor. Some rooms are maintained negative to both corridors for safety reasons (containment of test article aerosols). Street areas (outside the barrier) are at the lowest pressure.

All animal room doors remain closed except for passage or for special purposes. While closed, the room is an isolated unit with virtually no airflow in or out except through that room's intake and exhaust ducts. An absolute (i.e., HEPA) filter is located in each room's intake duct to remove airborne particulate contaminants. To ensure entrapment of any potentially noxious particulate release within a given room, exhaust air passes through two successive HEPA filters before being exhausted from the building. Single HEPA filters are located in the exhaust ducts of each room; the second filtration occurs just before the air leaves the building.

Room temperatures are individually adjustable and are automatically recorded and monitored in a central location. Room temperatures generally fluctuate no more than ±2°F. Temperatures are recorded at 60-minute intervals on a remote chart recorder and an alarm system makes immediate contact with responsible personnel on a 24-hour basis should temperatures be less than 72°F or greater than 78°F. Lights, controlled by automatic timers, are routinely set on a 12-hour light/12-hour dark cycle.

The cage washing area is divided into a clean and dirty side. Positioned in the wall separating the two sides are a large pass-through cage and rack washer, a smaller cage and bottle washer, and a pass-through autoclave. A second autoclave located in the clean wash area will accommodate large racks with cages or bulk supplies. Both autoclaves operate to 270°F, have digital timers and a three-pulse vacuum.

All animal watering in the facility, except for special purposes, is by means of automatic water systems attached to the cage racks. Nearly all racks and cages used in the facility, including attached automatic watering systems, are autoclavable.

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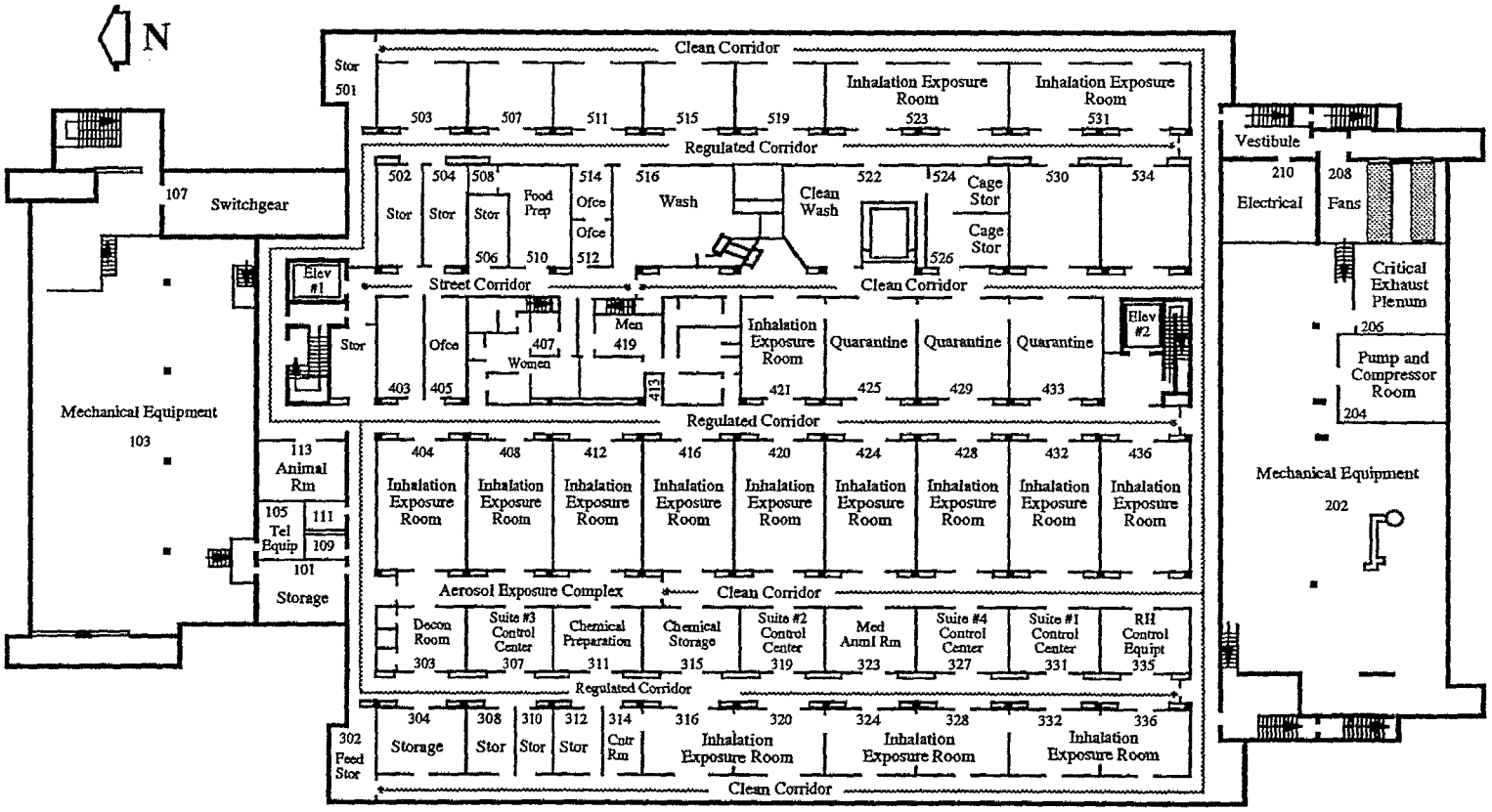

FIGURE V-1. Life Sciences Laboratory-II Basement Floor Plan

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Animal drinking water is provided by the city of Richland's system. Water quality is monitored, as required by state and federal regulations, by the city of Richland. In addition, LSL-II animal drinking water is analyzed for contaminants at least once each year. We do not acidify or chlorinate animal drinking water; however, the water is chemically softened and filtered to remove excess minerals. The sodium ion concentration in the softened water is approximately 50 ppm.

2. Animal Care Procedures

The operation of the LSL-II animal facility is focused on maintaining animals in a clean, stable environment and maintaining them free of infectious diseases. Sanitation and barrier procedures are well-defined and strict adherence to these procedures by all personnel is enforced throughout the facility.

Barrier procedures for the facility provide two levels of control. The first level is designed to prevent introduction of pathogenic microorganisms into the facility. If this should fail at any time, the second level provides good protection against movement of the pathogen from one room to another within the facility.

a. Preventing Introduction of Pathogens into the Facility

(1) Animal Control. The first level of control begins with careful selection of sources of pathogen-free stock and limiting those sources to reduce the risks of introducing pathogens from a supplier. Limiting the sources also generally provides better control over transportation arrangements and thus potential exposure to pathogens in transit. Animals arrive at the nearby Pasco airport and are promptly picked up in one of two climate-controlled BNW animal transport vehicles.

Our health-screening procedures have been reliable for detecting the presence of pathogens in incoming animals. Bacterial culture, serologic testing, and microscopic examination of selected tissues are used to detect pathogens and lesions in the animals examined. Our usual procedure is to promptly kill all animals in the group if a pathogen is found that is judged significant with respect to its possible effect on the study for which the animals are to be used or on other ongoing studies in the facility.

(2) Control of Personnel, Equipment, and Supplies. Our barrier procedures strictly control movement of personnel, supplies, and equipment into and within the facility. Personnel entry is limited to a "need-to-go" basis. Equipment must be thoroughly sanitized before entry and once in, generally remains within the barrier area. Supplies are removed from outer shipping packaging and sterilized, if appropriate, before passing into barrier areas.

b. Preventing Pathogens from Moving from One Room to Another in the Facility

(1) Personnel Control. The LSL-II animal facility is operated to allow for some difference in the extent of barrier protection for individual rooms. However, all animal rooms, including quarantine rooms and animal exposure rooms are operated according to our clean room regulations. Access into these rooms is only from the clean corridor. Personnel are required to wash hands and arms (or shower) and change into sterilized clothing before entering the clean corridor. Exit from animal rooms and animal exposure rooms is permitted only into the regulated corridor. Once out of the room, re-entry is permitted only by way of the clean corridor after a clothing change and hand and arm wash in the change room. When exiting a quarantine room, personnel must return directly to the change room, remove their clothing and wash their hands and arms before proceeding to any other area.

(2) Animal Control. Animals are not permitted in the clean corridor. Therefore, animals are moved from the quarantine room to the exposure room in the regulated corridor. The transfer is made in closed 2.3-m^3 whole-body exposure chambers. The transfer chambers are moved through the regulated corridor to the side of exposure room doors, then chamber doors are opened and the cage units are transferred through the exposure room doors to a clean rack in the exposure room or adjacent animal

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room, if housing is not in the exposure room. For the studies proposed, the animals are expected to be quarantined in the same rooms in which they will be held after exposures start.

All operations with rodents in the facility are designed to avoid the necessity of moving animals through the corridor for exposure or other experimental procedures and then returning them to the animal housing room. For these studies, this will be accommodated by providing a door in the corridor to create a suite between adjacent rooms that are to be used for housing and exposure.

Animals from ongoing studies within the facility are monitored for pathogens using serologic, culture, and direct examination methods. Besides providing data for individual studies, this information is used for pathogen control within the facility.

(3) Control of Equipment and Supplies. Equipment is washed in the cage washer and sterilized or sanitized as thoroughly as possible before being moved through the clean corridor into an animal room or animal exposure room. Soiled animal racks and cages are moved through the regulated corridor to the wash area. When practical, other equipment is dedicated to a room and remains there as long as it is needed. Sanitation procedures for such equipment are carried out in the room. If it must leave the room, exit is via the regulated corridor.

c. General Sanitation Procedures. Floors in all animal rooms, animal exposure rooms, and corridors are sanitized daily. Animal room and exposure room floors are hosed off once a day with NPD UNICIDE 128 (a sanitizer containing quaternary ammonium compounds) solution in 100 ± 10°F water. Corridor floors are washed once per day using the NPD UNICIDE 128 solution in a mechanical floor scrubber. More thorough scrubbing of floors and walls in rooms and corridors is done on an as-needed basis.

All cages and cage racks are washed every 7 days when in use. Cleaning agents dispensed during various washing cycles of the cage and rack washer (Better Built, Model 6300 SP) are Uri-Solv, pH Control, and PRL-18. These are all products of Pharmacol Research Laboratories, Inc. The initial cycle is with Uri-Solv, a phosphoric acid solution used to remove mineral deposits. After the first cycle, pH Control, a sodium hydroxide solution, is added to neutralize the acid. PRL-18, a chlorinated alkaline cleaner, is added to the second (last) wash cycle. This cycle is followed by two thorough rinse cycles using fresh, clean, ~180°F water. After washing, animal equipment is held in a clean storage area. When needed, it is moved through the clean corridor to the exposure room or animal room. All excreta pans beneath the mouse cage units are removed every morning and replaced with clean pans that have been washed in the cage washer.

The LSL-II animal facility is maintained free of wild rodents and other vermin by facility design and construction features, and by controls on the movement of equipment and supplies into the animal facility. No pesticides are used in the facility.

3. Animal Care and Use Committee and Accreditation by the American Association for the Accreditation of Laboratory Animal Care (AAALAC)

BNW has an Animal Care and Use Committee (Dr. Rowe, Chairman) with representation from each organizational group within BNW that uses animals. The Legal Department is also represented on the Committee. The Committee's non-BNW affiliated member is a biologist-educator from a local elementary school. Initiation of all studies involving the use of animals is dependent on the Animal Care Committee's review and approval. Committee functions have been defined in the Animal Welfare Assurance Statement submitted to the Office for Protection from Research Risks, National Institutes of Health (NIH). Our PHS (NIH) assurance number is A 3353-01; our USDA registration number is 91-R-006.

BNW's Animal Care Program (and facilities) has had continuous full accreditation by AAALAC since 1976. The next AAALAC site visit will be in 1994.

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VI. GLP COMPLIANCE

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VI. GOOD LABORATORY PRACTICES COMPLIANCE

Except where deviations are specified by the contract, these studies will be conducted in compliance with the EPA Good Laboratory Practices (GLP) regulations, 40 CFR 792.

A. GOOD LABORATORY PRACTICES (GLP) IN THE TOXICOLOGY DEPARTMENT

BNW has a QA Unit that resides in the Life Sciences Center. It is staffed by two full-time auditors and two clerks who report directly to the Manager of Operations in the Life Sciences Center. The QA Unit staff is responsible for providing independent verification to management that the testing facility is in compliance with relevant regulations. In fulfilling this responsibility, the QA Unit monitors compliance with those regulations and BNW SOPs through surveillances, audits, and data reviews. Written reports of compliance, which note any problems and corrective actions taken (§792.35), are then submitted to Task Leaders involved, Line Management in the Toxicology Department, and the Manager of Operations.

B. GOOD LABORATORY PRACTICES FOR THE PROPOSED PROJECT

1. Personnel

The Principal Investigator (PI) has the requisite education, training and experience to conduct the proposed studies. He represents the single point of control and has the overall responsibility for the technical conduct of the studies. The Study Director is responsible for the day-to-day decisions that involve the study, as specified in §792.33. All Task Leaders responsible for specific tasks have the education and experience necessary for their assigned functions. Technicians have, or if necessary will receive, training in the specific areas in which they will be working.

2. Facilities

In compliance with 40 CFR 792, BNW management will assign adequate facilities suitable for the proposed work. Animal facilities are operated in compliance with all applicable regulations.

3. Quality Assurance Unit

a. Surveillances and Audits. The QA Unit staff will monitor study activities through routine surveillances and data audits in compliance with the GLP regulations [§792.35(b)]. Study activities that will be reviewed during surveillances include: animal receipt, quarantine, health screen and release to study, randomization, and identification; exposure; calibration of the exposure system; body weight measurement; clinical observations; computer data collection; clinical pathology; special studies (ophthalmologic exams, minute volumes, EKGs, blood pressure measurements, etc.); necropsy; tissue trimming; and slide preparation. During the surveillance activities, conformance to study protocol, SOPs, and other applicable standards is assessed. The methods used in conducting surveillances are detailed in the SOP, *Inspection of Study Activities*.

The study protocol will be reviewed and signed by the QA Auditor. In compliance with §792.35(b), study data will be audited quarterly or, as in the case of one-time events, when generated. Data to be reviewed include: protocol amendments and deviations; exposure; body weights, clinical observations, clinical pathology, special studies, system calibration, mortality, necropsy, and histology; pathology, wet tissues, and slide/block match-up. Each set of data will be reviewed for compliance with the study protocol, SOPs, and applicable Sponsor-generated Statement of Work requirements. The Development Phase and Prestart Report, and the Final Study Report will be validated with the raw data. Audit procedures and report validation are described in the SOPs *Protocol Amendments*, *Data and Report Audits*, *Pathology Data Audits*, and *Exposure Data Audit*.

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b. Auditor Training. BNW selects staff with technical experience for the QA Unit. The present members of the QA Unit staff have laboratory experience ranging from 13 to 20 years. This knowledge is augmented with a continuing education program of internal and external training seminars and classes. The QA Unit staff participate in the in-house training provided to the technical staff. In addition, they attend meetings in which the study activities and problems are discussed so that they can be better informed about the activities and data they are reviewing.

The staff of the QA Unit have attended various local courses of QA given by Columbia Basin Community College and the Quality Training and Resource Center (a multicontractor organization designed to provide comprehensive training in QA, Safety, and Environmental Compliance). Each year BNW provides funds for the auditors to attend annual meetings and associated training seminars of the Society of Quality Assurance. Ms. Gelman is an American Society of Quality Control (ASQC)-certified Quality Auditor.

c. Quality Assurance Procedures. The QA Unit has SOPs that address surveillances, auditing activities, record maintenance, and record control. These SOPs are reviewed annually and updated as needed. The process of SOP maintenance is described in the next section.

4. Standard Operating Procedures

BNW has a defined SOP process, which is described in SOP, *Production and Use of Standard Operating Procedures*. Procedures for study activities are prepared by the professional staff and approved by BNW Line Management prior to the start of the study. They are reviewed annually and again when established procedures are modified. The QA Unit retains a current copy of all SOPs and maintains the historical file of retired SOPs.

Official copies of new or revised SOPs are issued to the workplace and the Task Leader by the QA Unit. An unofficial copy, with a signature sheet, is routed for review to all staff who will be using the SOP. Group training sessions are routinely held to discuss the particulars of SOPs (including any changes), then individual "hands on" training is provided by the Task Leader (or designee), as needed, to assure the staff is well-versed and proficient in conducting the procedure. Any deviations to SOPs during the course of the study must be authorized by the PI (or his designee).

Conformance to SOPs is monitored during QA Unit surveillances and audits. Deviations from standard procedures are discussed with the PI and described in the QA Unit report to Line Management.

5. FDA Inspections

The most recent FDA inspection at BNW was conducted August 1992. The laboratory was in compliance with 21 CFR 58.

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VII. CAPABILITY & MGMT PLAN

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VII. ORGANIZATION, EXPERIENCE, CAPABILITY AND MANAGEMENT PLAN

A. BATTELLE, PACIFIC NORTHWEST LABORATORIES (BNW)

Battelle Memorial Institute was created in 1923 by the will of Gordon Battelle, an Ohio industrialist. Since then it has become one of the world's largest independent, not-for-profit research organizations, with major laboratories in Columbus, Ohio; Richland, Washington; Geneva, Switzerland; and Frankfurt, Germany.

BNW, a major component of Battelle Memorial Institute, is a well-established, experienced, multidisciplinary contract research organization located in Richland, Washington, with a scientific staff and supporting personnel of more than 4000 employees. Figure VII-1 shows the organizational structure of BNW. The Toxicology Department within the Life Sciences Center (Figure VII-2) will have the responsibility for the Philip Morris projects.

Over the past decade, BNW has made a commitment to focusing on inhalation toxicology as a center of excellence within Battelle. As a research facility, BNW believes that its expertise can most effectively be directed to performing studies requiring the inhalation route of administration, and therefore we have directed our attention to refining our capabilities in this area. A large investment has been made by BNW over the past several years in facility modifications, purchase and design of state-of-the-art automated exposure systems, analytical instrumentation, and in training and educating personnel involved in inhalation toxicology studies.

An Inhalation Toxicology Program Office was established within the Toxicology Department to increase the emphasis of the Department on the inhalation toxicology technical and project management areas for increased responsiveness to government and industrial sponsors.

The above factors combine to demonstrate that BNW management, technical and support staff are dedicated to providing the highest quality services and results to the client in the conduct of inhalation toxicology studies at BNW.

B. TOXICOLOGY DEPARTMENT

The Toxicology Department (whose organizational structure is shown in Figure VII-3) is part of the Life Sciences Center. The department has a staff of approximately 120 people working in laboratories and offices covering more then 100,000 ft^2 located in the LSL-II building. Over the past several years, this department has developed a national and international reputation as a center of excellence in inhalation technology and toxicology.

C. PERTINENT EXPERIENCE

Research and development in vapor and aerosol exposure system technology within the Toxicology Department is carried out by a team of scientists, engineers, specialists and technicians. The staff, with overlapping backgrounds in physics, chemistry, inhalation toxicology, toxicologic pathology, radiation biology, computer science and a variety of engineering disciplines, share a basic interest in inhalation technology and have developed and tested exposure systems for animal exposure. Among these developments are two innovative whole-body inhalation exposure chambers (U.S. Patent #4,216,741) and a nose-only inhalation exposure system (U.S. Patent #4,721,060). Other inhalation exposure techniques developed in our laboratory include: steady nebulization of small samples of material; monodisperse aerosol generation from liquids, solids, and vapors; generation of a solid carrier aerosol for oils and chemicals; generation of highly respirable concentrations of fly ash; aerosol generation methods, such as electrostatic generation and nonaqueous nebulization, and an inexpensive method for on-line size fractionation. We have also expanded our capability to measure specific surface, density and dissolution characteristics of aerosol particles.

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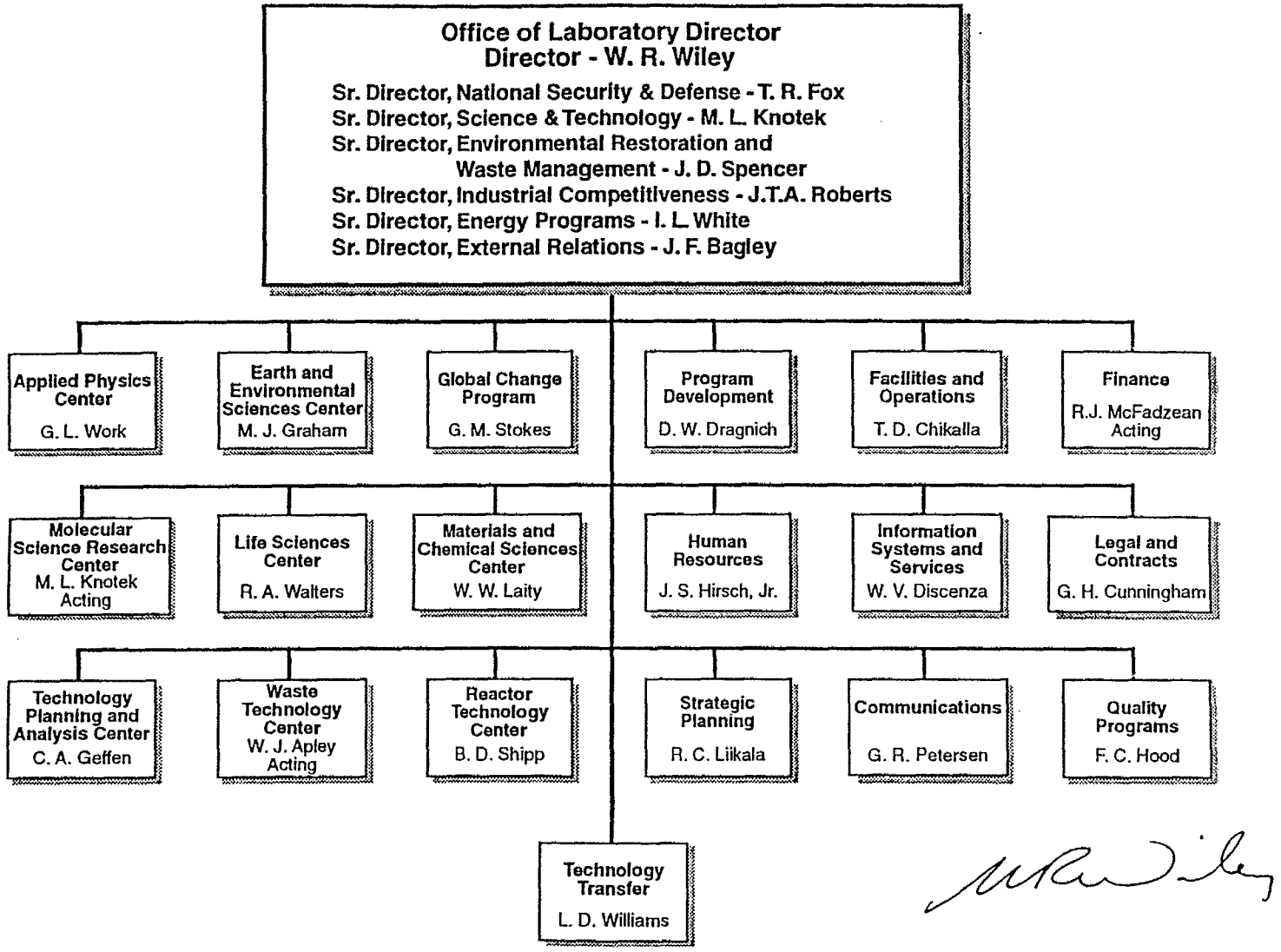

FIGURE VII-1. Organizational Structure of Battelle, Pacific Northwest Laboratories

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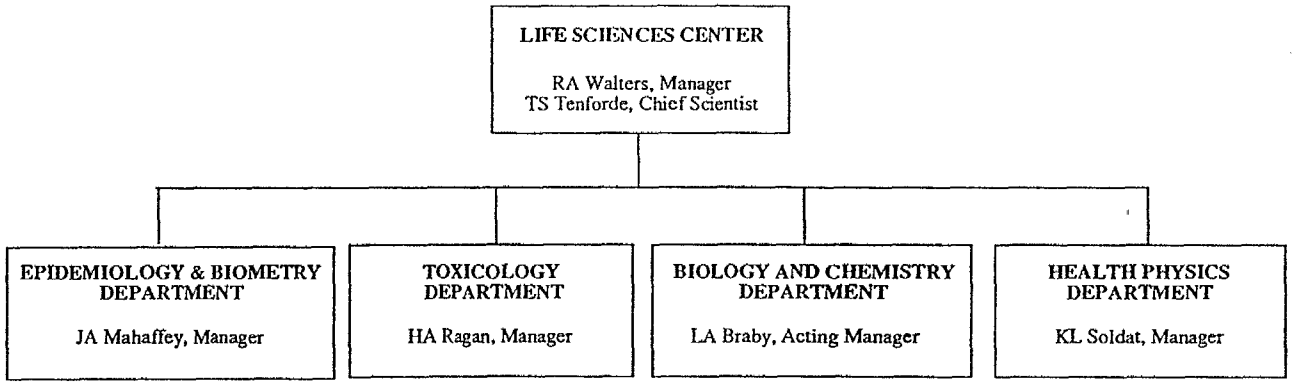

FIGURE VII-2. Organizational Structure of the Life Sciences Center

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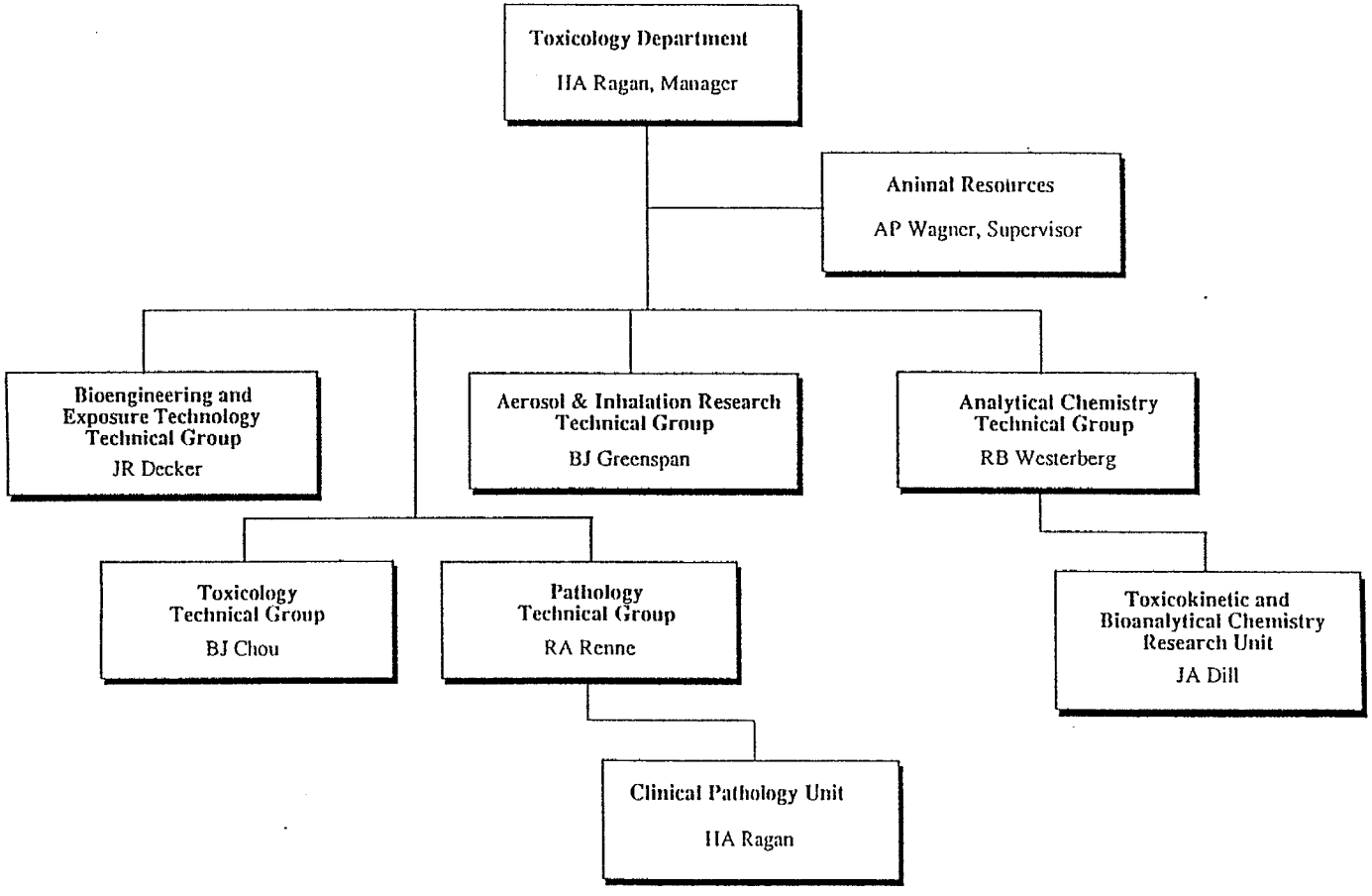

FIGURE VII-3. Organizational Structure of the Toxicology Department

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Scientists at BNW have been conducting animal inhalation studies for more than 25 years. NTP studies of more than 40 chemicals have been or are being investigated for acute, repeated-dose, subchronic, and chronic toxicity, and carcinogenicity in Fischer-344/N rats and B6C3F1 mice. NTP-sponsored inhalation teratology studies in CD-1 mice and Sprague-Dawley rats have been completed on eight chemicals.

Previous inhalation toxicology projects include: inhalation bioassays of cigarette smoke; and health effects of inhaled volcanic ash (National Institute of Environmental Health Sciences; NIEHS); studies in which rats and rabbits were exposed to organic vapors for teratologic studies and others in which hamsters were exposed to fibrogenic dust by intratracheal instillation to determine the role of pulmonary fibrosis in the etiology of lung cancer; development of oil shale aerosol technology (DOE); effects of prolonged inhalation of nickel-enriched fly ash in Syrian Golden hamsters (EPA); pulmonary deposition, translocation, and clearance studies with neutron-activated inhaled dusts; biological effects of inhaled sulfur pollutants (EPA); inhalation hazards to coal miners (DOE); the cross-placental transfer of metallic air contaminants (EPA). Other animal studies have involved pulmonary effects of pellets containing cigarette-smoke condensate implanted in the lungs of rats (National Cancer Institute; NCI).

Inhalation toxicology studies associated with our work in nuclear energy, which are sponsored by the U.S. Department of Energy (DOE), include: 1) aerosol and analytical technology development; 2) cocarcinogenic effects of uranium mine air pollutants (radon daughters, ore dust, cigarette smoke) in rats and dogs to determine the etiology of lung cancer in uranium miners; 3) major programs on the pulmonary and skeletal carcinogenesis of inhaled soluble or insoluble plutonium and other transuranic elements; 4) toxicity of plutonium and other radionuclides in the fetus and neonate; 5) radionuclide metabolism in preexisting disease states; 6) toxicity of noble gases associated with reactor operation, and of elements of the thorium fuel cycle; and 7) the effects of plutonium-sodium aerosols.

BNW has extensive experience with nose-only exposures of rodents as well as other animals including dogs and miniature swine. Rodent nose-only exposures completed in the last 5 years include several cigarette smoke studies, plutonium-238 oxide aerosol, promethium and cesium silicate aerosol, nitropyrene, and glycerol aerosol. The nitropyrene and glycerol exposures were conducted for 6 hours per exposure period. All other exposures required confinement of the animals for shorter periods of time. BNW has developed nose-only exposure technologies that assure fresh exposure material to each animal and assure that there is minimal heat stress to the animals confined in the animal holding tubes.

In addition to our government-sponsored studies, several major inhalation toxicology programs are supported, or have been supported, by private industry. For confidential reasons, the name of the clients and type of studies are not listed.

D. PROJECT MANAGEMENT PLAN

The proposed project will be conducted in BNW's Toxicology Department. The planned project organization (functional) is shown in Figure VII-4. BNW operates with a matrix management system because of the nature of contract research with multiple sponsors and the multidisciplinary approach to research. This system frees the Principal Investiagtors to devote their full attention to project management rather than being diluted by additional concerns required by line management responsibilities.

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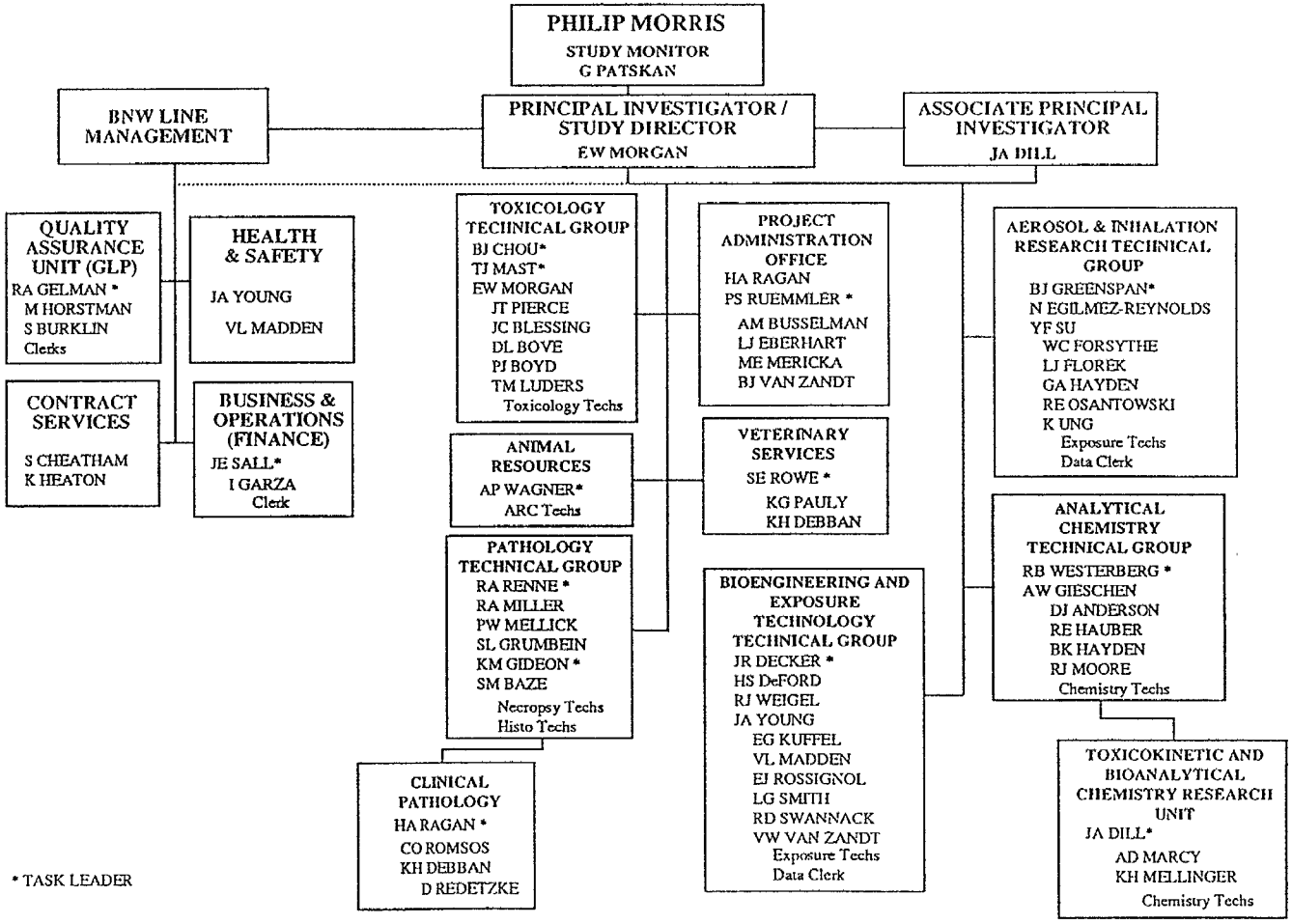

FIGURE VII-4. Organization Structure of the Philip Morris Project

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E. RESPONSIBILITIES AND AUTHORITY OF THE PRINCIPAL INVESTIGATOR

The PI for Philip Morris-sponsored studies, Dr. Morgan, is administratively within the Toxicology Department. Dr. Morgan will be responsible for scheduling, coordinating, monitoring, and reviewing the progress of technical activities, including toxicology, pathology, animal care, veterinary laboratory services, exposure engineering, aerosol physics, analytical chemistry, clinical pathology, and health and safety. He will be the focal point for all program communications within BNW, and will work with both the technical staff and contract group of the Sponsor in coordinating work scopes and changes for the various contracts. Dr. Morgan is also responsible for budgetary and fiscal control of all Philip Morris contracts. He will be responsible for establishing fiscal procedures and monitoring bi-weekly cost accounts and labor summaries provided by the BNW business office.

Within the Philip Morris programs, Dr. Morgan will be in daily communication with the Task Leaders and will hold more formal meetings at least biweekly with the Task Leaders and QA Unit (QAU) to discuss progress, potential technical problems, milestone schedules, and the status of costs versus technical progress.

As PI, Dr. Morgan will have the following authorities and responsibilities of control over all staff members working on Philip Morris projects:

- Direct control, including approval for expenditures of project funds
- Concurrence with the assignment or removal of project staff
- Concurrence with facilities assigned to Philip Morris projects
- Performance evaluations of project staff in their annual staff development reviews by management, including recommendations for promotion
- Recommending, when required, oral and/or written reprimands to staff assigned to the Philip Morris projects
- Reporting unsatisfactory performance of assigned staff to Department Management, and insisting that corrective action be taken
- Approving study protocols, data forms, technical reports, and all other documentation related to the Philip Morris studies
- Specifying appropriate, and timely correction of deficiencies or problems detected by QA and other project staff
- Defining, documenting, and communicating the responsibilities and authorities of staff assigned to the Philip Morris projects
- Assigning supervisory and task leadership responsibilities for weekends, holidays, and vacation periods to assure that qualified professional personnel are available in case an off-normal event should occur
- Conducting an Operational Readiness Review (ORR) with Task Leaders, QA, and Department Management prior to the initiation of animal exposures to include a review of the Study Protocol and SOPs, an analysis of the exposure system, and discussions of potential problem areas or health and safety concerns

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- Conducting frequent meetings with Task Leaders to review compliance with Protocols and SOPs and discuss the various aspects of conducting these studies

- Communicating with the Philip Morris Study Monitor concerning progress, technical concerns, or potential problems.

F. DAILY MONITORING OF THE STUDY EVENTS

As soon as the study protocol is approved and the starting date is determined, the schedule of study events for the Test System (Toxicology, Veterinary Care, Pathology, and Special Toxicology Studies) is compiled into a computer system. Each month the study events will be printed on a monthly calendar form (Figure VII-5), and distributed to the Task Leaders and PI for monitoring and assessing the progress of the study. These schedules will also be used to forecast the staffing requirements. Similar monthly schedules are also prepared for the Test Article (Exposure System, Exposure Generation and Chemical Analysis and Monitoring, Exposure Operations Events, and Chemistry Operations Events).

G. MONITORING PROJECT COSTS AND CONTRACT MODIFICATIONS

As soon as the contract has been awarded, a total project budget and detailed work breakdown structure will be prepared and entered into a computer. Monthly cost reports are used by the PI and Task Leaders to monitor the project costs and commitments. Task Leaders are responsible for providing detailed descriptions for any variances from the original estimates that have not previously been covered by contract changes or modifications.

These variance analysis reports will be used to alert the Sponsor of any additional funding needs as soon as they have been noted.

Contract modifications are automatically assigned an action number by the BNW Contract Associate at the time of receipt. The PI and Department Administrator are alerted of the change and action number on the same day. Cost details and schedule impact are determined by the affected Task Leaders and provided to the Department Administrator who works with the PI, BNW finance and contract personnel in preparing the final proposal. Once a Modification has been defined, the budget, estimated labor hours and schedule details are adjusted accordingly so that all project management information is kept current.

H. MILESTONE SCHEDULES AND DELIVERABLES

A schedule of events and deliverables is prepared at the beginning of each study and entered into a master schedule program maintained by the Department Administrator. Reminders of upcoming events and milestones are sent to all Task Leaders well in advance of the event. Changes in schedules are easily analyzed by this computerized approach, which also provides an effective method of scheduling personnel and facility needs of several projects going on at the same time.

A Phase 1 report will be prepared detailing the construction of the system and prestart testing to define system operating parameters. Interim study reports will be prepared after 12 and 18 months for the chronic study. A final report will be submitted within 12 months of completion of the study. Study report(s) will be prepared for the subchronic and any mechanistic studies performed.

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SAT.	SUN.	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
1	2	3 Week of Animals to Arrive Body Weights- 1 Day after Arrival	4	5	6	7
8	9	10 Acclimization to Exposure Tubes Health Screen to AR Lab	11 Acclimization to Exposure Tubes Day -6 Body Weights	12 Acclimization to Exposure Tubes	13 Acclimization to Exposure Tubes Randomization Wts, Group Assignments, & Identification	14 Acclimization to Exposure Tubes
15 Acclimization to Exposure Tubes (if needed)	16 Acclimization to Exposure Tubes (if needed)	17 Day 0 Body Weights	18 RASS Male and Female Day 1 Body Weights & Observations RASS First Exposure Day	19 Sham and Diesel Control Day 1 Body Weights & Observations Sham and Diesel Control First Exposure Day	20	21
22	23	24 Week of VAS Animals to AR Lab	25 RASS Week 2 Body Weights & Observations	26 Sham and Diesel Control Week 2 Body Weights & Observations	27	28
29	30	31	**April 1** RASS Week 3 Body Weights & Observations	**April 2** Sham and Diesel Control Week 3 Body Weights & Observations	**April 3**	**April 4**

FIGURE XII-5. Monthly Study Calendar

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The Toxicology Department Archive is a limited access facility within LSL-II. A Senior Administrative Assistant oversees the day-to-day activities of this office. All original source technical records generated on the Philip Morris studies will be filed in this office. The SOP "*Data Handling and Storage of Study Documents and Materials*", covers records management during conduct of the study. At the completion of the Study Report, personnel from the Program Office perform final verification of the completeness and accuracy of the file records. If records are determined to be missing and a thorough search does not locate the data, a missing record form is completed and inserted in the appropriate file folder. A list of the missing records is retained in the Program Office and every attempt is made to locate the missing documents after the rest of the data is forwarded to the Sponsor's archives.

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VIII. QUALIFICATIONS OF PERSONNEL

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VIII. QUALIFICATIONS OF PERSONNEL

A. KEY PERSONNEL

Below are brief statements regarding experience and accomplishments of key, critical, and supporting individuals who are germane to the project and their proposed roles for these studies. Complete resumes for key personnel are included in Appendix B. BNW understands the named personnel are necessary for the successful performance of this contract. If substitutions become necessary, BNW will provide a detailed explanation of the circumstances necessitating the substitution to the Sponsor's Study Monitor. The proposed substitutes will have substantially equal abilities and qualifications to those of the person being replaced.

1. Principal Investigator--E.W. Morgan

Dr. Earl W. Morgan received a BS in Agriculture with a science emphasis, and a DVM degree from the University of Missouri in 1973 and 1976, respectively. From 1976 to 1981, Dr. Morgan was in the U.S. Air Force Veterinary Service. From 1981 to 1983, he was in private practice in Missouri and Oklahoma.

In 1983, Dr. Morgan entered the U.S. Army and was assigned to Letterman Army Institute of Research (LAIR) at the Presidio of San Francisco, CA. From 1983 to 1987, he was assigned to the Mammalian Testing Section of the Division of Toxicology, initially as PI and for the last 2 years as the Chief of the section. He was an investigator for toxicological studies conducted in compliance with FDA and EPA Good Laboratory Practices regulations.

From 1987 to 1990, Dr. Morgan was working on a PhD in Toxicology at the University of Kansas Medical Center in the Department of Pharmacology and Toxicology. Dr. Morgan's research project involved the purification and characterization of the function and regulation of two isozymes of a rat liver microsomal carboxylesterase. The major techniques used were microsomal preparation, column chromatography, gel electrophoresis, Western immunoblotting, and enzyme kinetics.

From 1990 to 1992, he served as the Chief of Aerosol Biology, Department of Pathophysiology, U.S. Army Medical Research Institute of Infectious Diseases. Dr. Morgan was responsible for the re-establishment of the aerosol toxicology laboratory at the institute. He provided aerosol support for studies involving toxins, antitoxin therapy, detection of aerosol particles, and efficacy studies for candidate vaccines against airborne exposure to both infectious agents and toxins including high-molecular-weight biological toxins.

Dr. Morgan joined BNW in February 1992. Since that time he has served as Toxicologist and/or Study Director for six studies which use both rodents and canines.

Dr. Morgan is board-certified by the American Board of Toxicology (1986) and the American College of Veterinary Preventative Medicine (1984). He is licensed by the Veterinary Medical Boards of New Mexico and Missouri. Dr. Morgan will serve as the PI and Study Director for the proposed studies.

2. Associate Principal Investigator--J.A. Dill

Dr. Jeffrey A. Dill is a Staff Scientist in the Analytical Chemistry Technical Group of the Toxicology Department. He received a BS in Chemistry from the University of New Mexico (1979) and a PhD in Analytical Chemistry from Colorado State University (1983).

Dr. Dill joined the Toxicology Department in 1987. His duties involve development and evaluation of analytical methodologies used in chemical characterizations and qualification of test atmospheres used

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in inhalation toxicology studies. He is also responsible for the design and conduct of toxicokinetic studies, and for designing and validating assay methods for test chemicals and metabolites in biological samples.

Since joining the Toxicology Department, Dr. Dill has provided technical oversight of the chemistry task on over 20 different inhalation toxicity studies, ranging from 2-week, repeated-dose studies through 2-year chronic studies. These studies have investigated the toxic effects of eight different organic and inorganic test chemicals in rats, mice, or dogs, employing either whole-body or nose-only inhalation exposure units; the majority of which have been aerosol studies. Dr. Dill has completed numerous toxicokinetic or tissue distribution studies, performed in support of inhalation toxicity studies for NTP other governmental and industrial clients.

Prior to joining the Toxicology Department, Dr. Dill was employed by Pacific Northwest Laboratory (PNL) in waste packaging studies for nuclear waste repository investigations. Before joining PNL, he worked for Rockwell Hanford Operations as the Solution Chemistry Laboratory Team Leader. His experience was principally in inorganic analysis of natural water samples, supporting nuclear waste repository investigations.

Dr. Dill is a member of the American Chemical Society (Division of Analytical Chemistry), the American Industrial Hygiene Association, and the American Association of Pharmaceutical Scientists. He will serve as the Associate PI in charge of the exposure system, exposure generation, and chemistry.

B. CRITICAL STAFF

1. Toxicologists--B.J. Chou and T.J. Mast

Dr. Chou, the present Technical Group Leader for Toxicology, will be responsible for assigning and coordinating toxicologists and specialists for the proposed studies. Drs. Mast and Morgan will be responsible for coordinating toxicology procedures, evaluations and reporting.

a. Dr. Billy J. Chou. Dr. Chou received B Vet Sci and DVM degrees from the National Taiwan University, an MS degree in Animal Nutrition and a PhD degree in Physiology from Kansas State University (KSU). He is a Diplomate of the American Board of Toxicology with more than 20 years of experience in industrial toxicology. He has extensive experience in safety assessment of industrial chemicals. These include the design, supervision, evaluation and reporting of the toxicity and target organ toxicity involving industrial chemicals and therapeutic agents in laboratory animals. Before joining Battelle, Dr. Chou was the Department Head of Toxicology and Animal Facilities at William H. Rorer, Inc. He was responsible for conducting and reporting all required animal toxicity studies for Investigational New Drug (IND) and New Drug Approval (NDA) submissions. He was also the Project Manager for "growth promotion" and "anticoccidial" projects. Dr. Chou joined BNW in November 1984 as the National Toxicology Program (NTP) toxicologist and assistant PI and assumed the PI position in January 1986. Since then, Dr. Chou has been the PI for 26 NTP chemicals.

b. Dr. Terryl J. Mast. Dr. Mast has a BS degree in Biochemistry and Biophysics, an MS in Agricultural Chemistry, and a PhD in Environmental Chemistry through the Environmental Toxicology Department, University of California (UC), Davis. In addition, she was a postdoctoral researcher in Developmental and Reproductive Biology from 1984 through 1985 at the California Primate Research Center at UC, Davis. She is currently a Staff Scientist in the Toxicology Department at BNW. Dr. Mast is a member of the Teratology Society, the Society of Toxicology, the American Chemical Society, and is a Diplomate of the American Board of Toxicology.

Dr. Mast joined BNW in 1986. Her research interests, in addition to general inhalation toxicology, are in the area of developmental and reproductive toxicology, mechanisms of developmental toxicity and distribution, and pharmacokinetics of toxicants.

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Dr. Mast functions as Study Director and toxicologist for some NTP projects at BNW and also serves as Task Leader for the sperm morphology and vaginal cytology evaluation (SMVCE) task. She is PI for the current effort on nose-only inhalation studies being conducted for a confidential client.

Dr. Mast joined BNW following 2 years of work in Developmental Toxicology at the California Primate Research Center, where she studied the teratology, pharmacokinetics, and placental transfer of valproic acid in nonhuman primates and rodents administered by oral gavage. Her interest in metabolism and maternal-fetal pharmacokinetics led to studies on the development of hepatic xenobiotic-metabolizing enzymes in the fetal monkey. She conducted an oral gavage study in rats to correlate teratological effects of the pesticide oftanol, with maternal plasma kinetics, cholinesterase activity, and metabolism during organogenesis. She designed and participated in a study correlating plasma levels and toxic effects of dibromodichloropropane (DBCP) administered to Rhesus monkeys in drinking water on the male reproductive system.

2. Pathologists--R.A. Miller, S.L. Grumbein, R.A. Renne, and P.W. Mellick

Dr. Miller will be responsible for the necropsy supervision and histopathologic evaluations of all mice on the proposed studies.

a. Dr. Rodney A. Miller. Dr. Miller received his DVM degree, with distinction, from Iowa State University in 1971. After 4 years of clinical practice, he was selected for a PhD program at Washington State University, where he obtained 4.5 years of experience in diagnostic pathology in the Washington Animal Disease Diagnostic Laboratory. Much of his diagnostic experience involved tumor diagnosis in a variety of domestic animals and rodents. His thesis research was concerned with the inter-relationship of diabetes and atherosclerosis in rabbits. After receiving his PhD from Washington State University in 1979, he joined BNW, where he has participated in a number of rodent studies, including long-term effects of inhaled acid aerosols in rats, late effects (carcinogenesis) of americium nitrate in rats, and rat mammary carcinogenicity of injected plutonium citrate. Dr. Miller has participated in several subchronic and chronic inhalation studies in rats and mice exposed to various solvent-refined coal products. Dr. Miller successfully passed the certifying examination of ACVP in September 1980. Dr. Miller has 12 years of experience in necropsy supervision and in histopathologic evaluations of tissues from rodents in prechronic and chronic inhalation studies for NTP. The many NTP-sponsored inhalation studies which Dr. Miller has evaluated include the prechronic and chronic inhalation studies of 1,3-butadiene and chloroprene, and the prechronic studies on isoprene, gallium arsenide, and gallium oxide. Dr. Miller will be responsible for necropsy supervision and histopathologic interpretation of tissues for these studies on this project.

b. Dr. Sondra L. Grumbein. Dr. Grumbein received her DVM degree from KSU in 1971. Following 2 years of clinical practice, she returned to KSU and completed a PhD program in Veterinary Pathology in 1977. During that time Dr. Grumbein was Veterinarian for the KSU Animal Resources Facility and monitored research animals and facilities campus-wide. After receiving her PhD, Dr. Grumbein joined the Pathology Faculty of the College of Veterinary Medicine with responsibilities in teaching, diagnostic service, and research.

In January 1979, Dr. Grumbein joined the faculty at the newly formed School of Veterinary Medicine at Oregon State University (OSU). She developed the general pathology course taken by first-year veterinary students in their third quarter, including both microscopic and gross pathology laboratories, and taught that course to the first three classes admitted to the OSU program. Dr. Grumbein also developed and taught an animal pathology course for non-veterinary students. The remainder of her time was spent in the Oregon Veterinary Diagnostic Laboratory, providing diagnostic services to clinical veterinarians as well as livestock, poultry, and pet owners. She was certified as a Veterinary Pathologist by the American College of Veterinary Pathologists (ACVP) in 1979.

In September 1982, Dr. Grumbein joined Battelle Columbus Laboratories (BCL), Columbus, OH, as Associate Manager of the Pathology Section. One year later she became Chief of Pathology, and in 1985,

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Manager of the Pathology Section, responsible for anatomic and clinical pathology operations, including 4 veterinary pathologists and 25 histology and clinical pathology technical staff. The majority of that operation's work consisted of rodent studies performed for NTP under GLP and other government sponsors. Dr. Grumbein was involved in proposal preparation and costing, as well as protocol development and scheduling. She reviewed the work of BCL pathologists and established the group's reputation for producing pathology data generally uncluttered by duplicate diagnoses and spurious trends. Dr. Grumbein also supervised necropsies and read numerous NTP prechronic and chronic rodent studies, utilizing either the TDMS computer system or XYBION for data capture and management.

In 1987, Dr. Grumbein joined Pathology Associates, Inc., (PAI) as Director of the North Carolina Division, and took over as PI of their pathology support contract with NTP. In that role she interacted directly with NTP Project Officers and pathologists to meet their needs under that contract. Dr. Grumbein managed a full-service histology laboratory in support of NTP, as well as an electron microscopy laboratory with both transmission and scanning capabilities. She chaired numerous NTP Pathology Working Groups for both prechronic and chronic studies. Dr. Grumbein completed several special pathology projects for NTP, the largest of which included review of slides from ~2,000 rats and 1,100 mice retrieved from NTP Archives. The results of reevaluation of the incidences of selected neoplasms in those rodents, along with other measurable factors such as size and number of section, were included in two papers published in *Toxicologic Pathology* by NTP. Other special pathology projects included reading step-sections of residual kidneys of male rats on a chronic study for proliferative lesions and reading sections of residual pancreas of rats for exocrine lesions. Dr. Grumbein also performed or supervised a number of reviews of residual wet tissues for untrimmed potential lesions.

In January 1990, Dr. Grumbein rejoined Battelle at its Pacific Northwest Laboratories and has since participated in two repeated dose, three subchronic, and four chronic NTP inhalation studies, including supervision of necropsies and histopathologic evaluation of tissues from rats on the subchronic inhalation study of glutaraldehyde and the chronic inhalation study of chloroprene. Dr. Grumbein has 10 years of experience in necropsy supervision and histopathologic evaluations of tissues from prechronic and chronic NTP rodent studies.

c. Dr. Roger A. Renne. Dr. Renne, the Technical Group Leader for Pathology in the Toxicology Department, is responsible for the coordination of the pathology tasks, including animal sacrifice, necropsy, histology, and histopathology. He holds a DVM from Washington State University, and is a Diplomate of ACVP. He has over 21 years of experience in the pathologic evaluation of tissues from experimental animals used on chronic toxicity and carcinogenesis studies.

Since joining BNW in 1976, Dr. Renne has been PI on several projects, including studies evaluating the fibrogenic and carcinogenic potential of particulate oil shale materials using repeated intratracheal instillation, and inhalation toxicity studies of H_2S and ammonia in rodents. He has also been responsible for histopathologic evaluation of pulmonary lesions in dogs exposed to cigarette smoke, and gross and microscopic evaluation of tissues from dogs exposed to carcinogenic doses of particulate radionuclides via inhalation, and gross and microscopic pathology of hamsters exposed to fibrogenic particulates. Dr. Renne was PI for an industry-sponsored dermal carcinogenesis project and was acting PI for the NTP project for 14 months. Dr. Renne has 14 years of experience in necropsy supervision and 18 years experience in histopathologic evaluation of tissues from rodents in the NCI/NTP carcinogenesis program.

d. Dr. Paul W. Mellick. Dr. Mellick received his DVM degree from The Ohio State University in 1962 and his MS degree in Veterinary Pathology from New York State Veterinary College at Cornell University in 1964. After 2 years of clinical practice, he entered the Veterinary Corps of the U.S. Army. After a 1-year tour of duty in Vietnam during which he established a Veterinary Diagnostic Laboratory for Vietnamese livestock and poultry, he returned to the Armed Forces Institute of Pathology where he completed residency training in veterinary pathology. He was certified as a Veterinary Pathologist by ACVP in November 1970. From 1970 to 1972, he served as Chief, Toxicology Division, U.S. Army Environmental

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Hygiene Agency, Edgewood Arsenal, MD where he conducted toxicology studies on chemicals important to the Army using all routes of administration including inhalation, and a variety of animal models including rodents, dogs, birds and primates.

In 1972, he entered the PhD program in Comparative Pathology at UC, Davis. His thesis research involved inhalation toxicology and pulmonary pathology in nonhuman primates exposed to ambient concentrations of oxidant air pollutants. After the completion of his graduate studies in 1975, Dr. Mellick returned to his military duties as Chief of Pathology at the Letterman Army Institute of Research, Presidio of San Francisco. During his 8 years in this assignment he directed and conducted pathology research on a variety of biomedical research projects in the fields of toxicology, safety and efficacy of blood replacement solutions, nutrition and experimental surgery. He organized and developed Letterman's toxicology research and testing program, the only GLP-compliant toxicology capability in the U.S. Army. He organized and directed a highly successful residency program in veterinary pathology. In 1983 and 1984 he served as Head, Veterinary Medicine Department, U.S. Naval Medical Research Unit #3, Cairo, Egypt, where he planned, directed and conducted research on infectious zoonotic diseases in Egypt and other Middle Eastern countries. He then returned to the Presidio of San Francisco and became the Deputy Commander, Letterman Army Institute of Research. In this assignment he planned, directed and managed scientifically diverse biomedical research programs with a staff of 250 and an annual budget of $14 million. Concurrently, he served as Veterinary Pathology Consultant to the Surgeon General, assessing veterinary pathology requirements for all Department of Defense laboratories worldwide; monitored training, career development and professional capability of approximately 60 military veterinary pathologists and made recommendations concerning appropriate veterinary pathology staffing to the Chief of the U.S. Army Veterinary Corps.

In 1987, Dr. Mellick retired from active military service to pursue interests in inhalation toxicology and pulmonary pathology at BNW. Since joining BNW, his primary responsibilities have been necropsy supervision and histopathologic evaluations of tissues from rodents in prechronic and chronic inhalation studies for NTP, and PI for inhalation toxicology studies for an industrial sponsor. He was the study pathologist for NTP-sponsored subchronic inhalation toxicity studies of gallium arsenide and isoprene in rats and glutaraldehyde in mice.

3. Clinical Pathologist--H.A. Ragan

Dr. Harvey A. Ragan is the Manager of the Toxicology Department, as well as the Director of the Clinical Pathology Laboratory within the department. Dr. Ragan has degrees in biology and in veterinary medicine, and has postdoctoral training in hematology. His special research interests are the interrelationships between pollutant metals and nutritional deficiencies on the hematopoietic and immune systems, the clinical pathologic effects of electromagnetic fields or internal emitters on experimental animals, and the *in vitro* quantitation of effects of pollutants on hematopoietic stem cells. Dr. Ragan has over 25 years of experience in laboratory medicine applied to beagle dogs, miniature swine, miniature goats, and laboratory rodents. He is a Diplomate of the American Board of Toxicology, a Past-President of the American Society of Veterinary Clinical Pathologists, a member of the American Society of Hematology, a member of the International Society of Animal Clinical Biochemistry, and a member of three task groups of the National Council on Radiation Protection. Dr. Ragan served as the PI/toxicologist for the NTP projects from February 1984 until December 1985, and has over 12 years of experience with NTP-sponsored toxicity studies. Dr. Ragan will serve as the clinical pathologist on the proposed projects.

4. Chemists--R.B. Westerberg, A.W. Gleschen, C.W. Wright, R.N. Lee, and S.D. Harvey

a. Dr. R. Bruce Westerberg. Dr. Westerberg is the Technical Group Leader for Analytical Chemistry. He received his PhD in Analytical Chemistry from Purdue University in 1974. He has a broad background and experience in bioanalytical chemistry, and characterization of test atmospheres in exposure chambers. As the Technical Group Leader for the Analytical Chemistry Group of the Toxicology

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Department, he is responsible for supervising personnel performing analytical and bioanalytical measurements.

Dr. Westerberg has acted as PI for a series of programs in which nicotine and cotinine were determined in plasma samples. He has also participated in Department of Energy (DOE) studies concerning the metabolism of complex mixtures. He has been chemistry task leader for numerous inhalation studies of a wide variety of test material including tobacco smoke, humectants, pharmaceuticals, various inorganic and organic aerosols, and numerous organic gases and vapors.

Before joining BNW, Dr. Westerberg was employed by E.I. DuPont Chambers Works, Jackson Laboratory, as an Analytical Research Chemist (1974-1980). During the early part of that period, he was responsible for the laboratory's HPLC facilities. Later he assumed responsibility for upgrading and operating the laboratory's GC/MS facilities. This work included quantitative analysis of industrial waste waters for trace levels of EPA-priority pollutants, and analysis for polychlorinated biphenyls (PCB) in complex organic materials. Dr.Westerberg is a member of the American Chemical Society (Division of Analytical Chemistry), the American Association of Pharmaceutical Scientists and the American Society for Mass Spectrometry.

b. Andrew W. Gieschen. Mr. Gieschen is a Senior Research Scientist involved in analytical organic chemistry in the Analytical Chemistry Group. He has a BS degree in Microbiology and Chemistry from Arizona State University (1983) and a MS degree in chemistry from Washington State University (1986).

He is an experienced chemist with expertise in trace organic analysis using high performance liquid chromatography and capillary gas chromatography. He has experience with GC/FID, GC/ECD, GC/TCD, GC/MS, HPLC/UV, and HPLC/Fluorescence techniques for analyses of environmental samples and samples obtained from biological matrices. Mr. Gieschen has in-depth knowledge of personal computer operating systems and electrical engineering. He also has a strong background in organic chemistry, organic synthesis, Fourier transform infrared spectroscopy, nuclear magnetic resonance spectroscopy, thin-layer chromatography, and low-pressure liquid chromatography.

Since joining the Toxicology Department in 1987, Mr. Gieschen has had the responsibility of supporting several NTP projects. His responsibilities include development, evaluation, and implementation of analytical methods for chemical characterization and quantification of inhalation exposure test atmospheres. He is also involved in the designing, validation, and implementation of analytical techniques used for bioanalytical and toxicokinetic studies. Since joining the BNW, Mr. Gieschen has been involved in the leadership and implementation of the analytical chemistry methods for over 20 inhalation toxicity studies involving more than 10 different chemicals. These studies have measured the toxicity of these organic compounds in rats and mice using whole-body and nose-only exposure units. Mr. Gieschen has also been responsible with the development of a highly automated HPLC analytical laboratory and implementation of a computerized automated on-line monitoring system.

Mr. Gieschen is a member of the American Chemistry Society, the Institute of Electrical and Electronic Engineers, and the American Association of Pharmaceutical Scientists.

c. Cherylyn W. Wright. Ms. Wright is an Analytical/Organic chemist specialized in sampling, extraction, and analysis techniques for trace organic analyses of solid, liquid, and gaseous sample matrices. She is an experienced separations chemist with expertise in gas and liquid chromatography with special emphasis in high-resolution gas chromatography using fused silica capillary columns. She has experience in the use of element-specific detection, as well as gas chromatography/mass spectrometry (GC/MS) and GC/Fourier transform infrared detection (GC/FTIR) for characterizing complex mixtures and compounds of interest from energy-related and environmental samples. In her graduate work, she developed a scheme to separate and identify sulfur-heterocycles from complex coal-liquid and shale-oil matrices.

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Since coming to Battelle, Ms. Wright has had experience in the separation, identification, and quantification of heteroatomic organic species in complex synthetic fuels, petroleum products, shale oils, diesel particulates, organic hazardous waste samples, aqueous leachates of organic matrices, shale waste waters, air pollution samples, and contaminated site environmental samples. She has directed the separation of coal-derived materials by chemical class fractionation for biological testing, as well as characterizing the class fractions chemically. In addition, she has directed the development of extraction and analysis procedures for specific compounds of interest from biological matrices such as urine, saliva, and plasma. This effort included analysis of plasma samples for nicotine and cotinine via fused silica capillary column gas chromatography with a nitrogen-specific detector. She has developed methods to monitor the stability and degradation of energy-related complex mixtures as well as specific compounds of interest used in inhalation toxicology studies. She has also been involved in the development of innovative sampling, extraction, and separation techniques for organic analysis including large volume air and water sampling, laboratory and in-the-field supercritical fluid extraction, and capillary zone electrophoresis.

d. Dr. Richard N. Lee. Dr. Lee has participated in the design and implementation of sample collection and analysis tasks conducted in support of several inhalation studies. This work has included a key role in the development of analytical procedures for the determination of trace levels of NO_x in an inhalation study involving co-administration of ozone and the tobacco-specific nitrosamine, NNK.

Dr. Lee has been trained as an inorganic chemist and has over 21 years experience in conducting trace gas and aerosol measurements in the ambient atmosphere. His experience includes the utilization of both continuous and integrated sampling techniques for the measurements of airborne materials. He has also conducted precipitation chemistry studies which have involved the measurement of inorganic and organic species in precipitation. These studies have focused on the acidic precipitation problem and the removal of hazardous organic pollutants, such as nitrobenzene and methylchloroform by rain. He has also developed and used special monitoring capabilities for measuring atmospheric tracer gases, hydrogen peroxide and volatile sulfur compounds in the atmosphere. Recently, he has been involved in trace organic analysis by GC/MS and sample preparation using supercritical fluid extraction.

e. Dr. Scott D. Harvey. Dr. Harvey joined Battelle after completion of his PhD degree the summer of 1988. Having pursued advanced training under two Tswett Medalist chromatographers, Professor R.E. Sievers (University of Colorado) and Professor M.V. Novotny (Indiana University), his primary interests reside in the application of high-resolution separation techniques for the isolation and identification of compounds in complex matrices.

Dr. Harvey's current interests center on the further development and application of high-resolution microcolumn HPLC, micellar electrokinetic capillary chromatography, and electroosmotically driven microcolumn HPLC techniques for studying the impact of environmental pollutants on biological systems. Specific interests include the delineation of metabolism associated with the detoxification of xenobiotic pollutants in plant systems and the ultratrace analysis of DNA adducts that result from environmental exposure to carcinogens. Carbon-fiber amperometric and semiconductor laser-induced fluorescence detectors are under development to allow attomole detection of DNA adducts. Related pursuits include microcolumn HPLC isolation of a variety of natural products arising from plant secondary metabolism (alkaloids and taxanes). These endeavors include multidimensional techniques and strategies for the resolution of enantiomeric forms which are often encountered in metabolic products. Dr. Harvey will participate in the protein/DNA adduct studies.

5. Exposure Technology Personnel--J.R. Decker, B.J. Greenspan, H.S. DeFord, and N.E. Egilmez-Reynolds

a. Mr. John R. Decker. Mr. Decker is the Technical Group Leader of the Bioengineering and Exposure Technology Group in the Toxicology Department. He holds a BS degree in Electrical Engineering from Colorado State University. Since joining Battelle in 1969, he has been

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instrumental in the development of a multitude of generation and monitoring systems for inhalation toxicology studies of aerosols, vapors, and gases, including cigarette smoke, radionuclide aerosols, fly ash, volcanic ash, military obscurants, pharmaceutical aerosols, diesel exhaust, and a multitude of organic vapors and inorganic aerosols. He has developed systems for monitoring and controlling the environment of animal exposure chambers. He has also developed several pulmonary function analysis instruments especially for small-animal studies. He contributed to the development of both the whole-body and nose-only exposure chambers presently used at Battelle for inhalation toxicology studies.

Mr. Decker engineered the automated data acquisition and control systems that monitor and control the basic inhalation test system functions including chamber airflow, vacuum, temperature, relative humidity, and chemical concentration.

b. Dr. Bernard J. Greenspan. Dr. Greenspan is the Technical Group Leader for the Aerosol and Inhalation Research Group in the Toxicology Department. He holds a BA with honors in Physics from Clark University and an MS and PhD in Biophysics from the University of Rochester Medical Center. Since joining BNW in 1985, he has been the exposure task leader for numerous aerosol and vapor inhalation exposures for NTP and pharmaceutical clients.

In addition to his work on inhalation toxicology, Dr. Greenspan is also involved in the design of new generation and delivery systems for pharmaceutical aerosols.

Prior to joining the staff at Battelle, Dr. Greenspan studied the toxicity of lithium combustion aerosols and the deposition and clearance of beryllium aerosols at the Lovelace Inhalation Toxicology Research Institute in Albuquerque, New Mexico.

From 1981 to 1983, he was a Staff Scientist in the Inhalation Department of Union Carbide Corporation's Bushy Run Research Center in Export, Pennsylvania. He was responsible for the design of aerosol and vapor exposure systems.

c. Mr. Henry S. DeFord. Mr. Henry S. DeFord is currently the Bioengineering and Exposure Technology Group Inhalation Exposure Engineer in the Toxicology Department. He holds a BS degree in Microbiology from the University of Washington and has studied engineering at Washington State University. Since joining Battelle in 1976, he has worked on the development of many test article generation and monitoring systems for inhalation toxicology studies of aerosols, vapors, and gases. He has designed components for monitoring and controlling the environment of animal exposure chambers. He has also been involved in the development of proprietary equipment and provides engineering support for non-inhalation research projects.

Mr. DeFords experience includes first-line supervision of daily exposure tasks as well as supervision of the design, purchase, and construction of exposure system components. He has worked closely with Mr. Decker in the design and development of inhalation exposure control systems at BNW.

d. Dr. Nazli Egilmez-Reynolds. Dr. Egilmez-Reynolds joined BNW in 1992 as a Senior Research Scientist in the Aerosol and Inhalation Research Group in the Toxicology Department. She holds a BE in Chemical Engineering from Aegean University in Izmir, Turkey, and a MSc and PhD in Chemistry (specialized in Aerosol Science) from Essex University in Colchester, England. She was also employed as a research worker for two years in Essex in the Aerosol Laboratory of Prof. C.N. Davies where she developed and characterized a nanometer aerosol generator and performed coagulation experiments using monodisperse and mixed aerosol systems. Her work developed the theory of coagulation of fine particles which was published in the Proceedings of Royal Society of London in 1982.

From 1983 to 1987, she worked as Research Scientist in the Product Research Group of the British-American Tobacco Company, Research and Development Center in Southampton, England. She was

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responsible for the Aerosol Laboratory and acted as the Chief Aerosol Scientist for the BAT group worldwide, coordinating research with associated laboratories in Louisville (US), Hamburg (Germany) and (Montreal) Canada. She developed and executed work programs on aerosol generation and behavior inside cigarettes, filters and human upper airways and participated in the Environmental Tobacco Smoke studies.

She worked as an independent Consultant on Aerosol and Tobacco Smoke between 1987 to 1992 and taught Chemistry as a Visiting Assistant Professor in the Chemistry Department of the University of Louisville between 1988-1991.

Since joining BNW last October, she has been the exposure task leader for three aerosol exposure studies.

6. Inhalation Technology

a. Inhalation Exposure Specialists. The Inhalation Exposure Specialists aid in design, supervise construction, and aid in test and evaluation of both hardware and software for inhalation exposure systems. They aid in generation, verification, validation, and the documentation for these systems. They train, supervise and schedule the activities of the Exposure Technicians in the routine operation, maintenance, and calibration of the exposure systems and in quality control activities. They are responsible for the daily review of exposure and environmental data and for assuring that Good Laboratory Practices are followed in the conduct of data collection. The Exposure Specialists aid in the compilation of data reports and in preparing technical input for proposals and scientific publications.

Name	Title	Years of Experience
LJ Florek	Inhalation Exposure Specialist	10
WC Forsythe	Inhalation Exposure Specialist	13
EJ Rossignol	Inhalation Exposure Specialist	19
RE Osantowski	Inhalation Exposure Specialist	1
K Ung	Inhalation Exposure Specialist	1

b. Engineering Specialists

The Engineering Specialists aid in the detailed electrical and mechanical design, supervise construction, and aid in test and evaluation of the exposure data acquisition and controls systems. The engineering specialists write, document and verify software for data acquisition and data analysis; provide routine maintenance and troubleshooting; prepare SOPs, and contribute to reports, proposals, and scientific publications.

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Name	Title	Areas of Responsibility	Years of Experience
EG Kuffel	Electronics Specialist	Design, fabrication, testing, maintenance of automated data acquisition systems for all NTP studies.	20
RD Swannack	Computer Program Specialist	Computer programming for data acquisition and data analysis for NTP studies.	11
VW Van Zandt	Computer Program Specialist	Computer programming for data acquisition and data analysis for NTP studies.	11
GA Hayden	Mechanics Specialist	Design, fabrication, testing, maintenance of exposure mechanical systems	6

c. Inhalation Exposure Technicians

The Inhalation Exposure Technicians are responsible for the daily control of the test article exposure; routine maintenance and calibration of the exposure equipment; and routine recordkeeping according to Good Laboratory Practices.

Name	Title	Years of Experience
GR Ell	Inhalation Exposure Technician	13
EM Milliman	Inhalation Exposure Technician	23
RD Devoir	Inhalation Exposure Technician	3
RV Lilienthal	Inhalation Exposure Technician	3
R Rodriquez	Inhalation Exposure Technician	3
KF Tarr	Inhalation Exposure Technician	6
RP de la Bretonne	Inhalation Exposure Technician	1
NZ Hertelendy	Inhalation Exposure Technician	1
CK Mullally	Inhalation Exposure Technician	1
DL Bowers	Inhalation Exposure Technician	1
SF Conley	Inhalation Exposure Technician	1

7. Laboratory Animal Medicine--S.E. Rowe

Dr. Stephen E. Rowe has a BS degree in Agriculture (biochemistry option) and a DVM degree from Purdue University, and an MS degree in Pathology from the University of Michigan. He is a Diplomate of the American College of Laboratory Animal Medicine and has 25 years of experience in laboratory animal medicine; 20 of those years have been at BNW. Prior to that, he completed a 2 ½ year training program in laboratory animal medicine at the University of Michigan where he received training and experience in the diagnosis of rodent diseases by clinical observation, by gross and histopathologic examination, and by laboratory culture and testing. Before that, he worked as an investigator on a variety of toxicology studies and directed animal care operations at the U.S. Army Environmental Hygiene Agency.

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